Diagnosing Mastocytosis: Cutting through the clutter

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Clinical manifestations and related mast cell mediators

Skin	
Pruritus	Histamine, PAF
Flushing	PGD_2
Urticaria	Histamine, PAF, LTC_4
Blistering	IL-6, tryptase, PGD_2, PAF
Constitutional	
Fatigue, weight loss, cachexia	Tumor necrosis factor-α, IL-1β, IL-6
Systemic	
Hypotension and swelling	Histamine, PAF, PGD_2 LTC_4, LTD_4, LTE_4 endothelin
Eosinophilia	IL-5
Mast cell proliferation	SCF, IL-3, IL-6, chymase
Fibrosis	Transforming growth factor-β
Inhibition of localized clotting	Heparin
Lymphadenopathy	IL-16, lymphotaxin
Gastrointestinal	
Increased gastric acid	Histamine
Intestinal cramping	Histamine, PAF, LTC_4
Skeletal system	
Osteoporosis	Heparin, tryptase
Lungs	
Bronchoconstriction	Histamine, PGD_2, PAF, LTC_4, LTD_4 endothelin
Mucous and edema	Histamine, PGD_2, PAF, LTC_4, proteases

PG, prostaglandin; PAF, platelet-activating factor; LT, leukotriene; IL, interleukin; SCF, stem-cell factor.

MC Carter, DD Metcalfe, HD Komarow 2014. Mastocytosis *Immunol Clin N Amer* 34

Supporting Evidence

- **Clinical**
  - Historical
    - Mast cell-mediator symptoms
    - Less atopic disease than general pediatric population
  - Cutaneous
    - Permanent pigmented lesions with a general distribution or diffuse thickening "peau d' orange" appearance
  - Other organ systems-mainly systemic disease
- **Laboratory**
  - Tryptase-reflects overall mast cell burden
    - May trend down over time and elevates with mast cell activation
  - Urinary metabolites-correlates with serum tryptase
  - Hematologic-Usually WNL; may see ↑ lymphs,↑ PT/PTT, ↑Plts
- **Sonographic**
  - Hepatosplenomegaly with systemic disease, rare lymphadenopathy

Differential Diagnosis: Pediatrics

Most Likely

- Diffuse or localized hyper-pigmented macules
  - Café au lait spots
  - Neurofibromatosis
  - Albright syndrome
- Bullous Lesions
  - Chronic bullous disease of childhood
  - Linear IgA dermatosis
- Solitary or multiple nodules
  - Congenital nevus
  - Juvenile Xanthogranuloma

Differential Diagnosis, cont.

Consider

- No lesions
  - Idiopathic flushing
- Diffuse or localized hyper-pigmented macules
  - Post-inflammatory hyperpigmentation
  - Secondary syphilis
  - Chronic urticaria
  - Atopic dermatitis
- Bullous Lesions
  - Staphylococcus infection
  - Drug eruption
  - Incontinentia pigmenti
  - Bullous pemphigoid
- Solitary or multiple nodules

Differential Diagnosis, cont.

Always Rule Out

- No lesions
  - Identifiable causes of anaphylaxis
  - Idiopathic anaphylaxis
- Diffuse or localized hyper-pigmented macules or papules
  - Scabies
  - Secondary Syphilis
  - Addison's disease
  - Lentigo
- Bullous Lesions
  - Bullous impetigo of infancy
  - Incontinentia pigmenti
- Solitary or multiple nodules
  - Leukemia
  - Lymphoma

Clinical symptoms/signs unlikely to be systemic mastocytosis or mast cell activation

- Hypertensive spells
- Symptoms that improve with medications not targeting mast cell mediators or their effects: Ex: medications for anxiety or depression
- Seizure activity; incontinence
- (Delayed) problems with memory
- Dementia
- Arthritic complaints involving small joints or involving muscles.
- Chronic hives; atopic dermatitis or eczema
- Delayed reactions to medications
- Rhinitis or rhinosinusitis
- Food allergy
- Non-anaphylactic reactions to beestings, fire ants, horseflies

Symptoms/signs with an increased likelihood of associated systemic mastocytosis

- Urticaria pigmentosa; positive Darier's sign
- Mast cell mediator-related symptoms:
  - Flushing/warmth/pruritus/abdominal cramps/diarrhea/bronchospasm/tachycardia/ (pre)syncope
  - The symptoms respond to epinephrine administration & administration of medications targeting mast cell mediators such as antihistamines, sodium cromolyn
- Anaphylaxis to bee stings
- Recurring episodes of tachycardia not responding to cardiac medications (β-blockers) or a pacemaker
- "Idiopathic" anaphylaxis
- Males with osteoporosis
- Eosinophilia
- Anaphylactic response to NSAIDs (90-95% of mastocytosis patients do tolerate them)

What are other common pitfalls when diagnosing mastocytosis?

- Carcinoid
  - Briefer flush, worsened by epinephrine vs beneficial epinephrine response in SM
- Common flushing/climacteric flushing
- Disorders of hyper/hypo hidrosis
- Spells-various types
  - 1. Endocrine (Ex: pheochromocytoma, thyrotoxicosis, medullary thyroid carcinoma, insulinoma, hypoglycemia)
  - 2. Cardiovascular (labile HTN, deconditioning, pulmonary edema, syncope, orthostatic hypotension, paroxysmal arrhythmias)
  - 3. Psychologic (somatization disorder, hyperventilation)
  - 4. Pharmacologic (withdrawal of adrenergic inhibitor, MAO treatment + tyramine, sympathomimetic ingestion, illegal drug ingestion, chlorpropamide-alcohol flush, vancomycin-red-man syndrome)
  - 5. Neurologic (postural orthostatic tachycardia syndrome, autonomic neuropathy, migraine headache, seizure disorders, stroke, cerebrovascular insufficiency)
- Panic attacks
- Simple faint; vasovagal episodes

A Word about Flushing

- Neurogenic-"Wet flushing"-sympathetic cholinergic neurons-stimulate sweat glands
  - Example: "Hot Flash"
- Dry flushing -direct vasodilation from vasoactive chemicals; no perspiration
  - Example: Histamine, kinins, prostaglandins, nicotinic acid, amyl nitrite
  - Most cases of "idiopathic" flushing

Laboratory pitfalls in diagnosing SM and a Shortcut Decision Pathway for ordering a Bone Marrow Biopsy

Common Laboratory Errors/Problems in Diagnosing SM

- Serum Histamine Measurements: samples must be processed rapidly
- Measuring the wrong mediator(s):
  - Urinary 5-HIAA-for diagnosing carcinoid
  - Urinary Metanephrines-for pheochromocytoma
- Bone Scans-nonspecific, nondiagnostic
- Measurement of urinary histamine
  - May only reflect commensal bladder bacterial production
  - Better to use urinary MIAA or n-Methyl histamine levels
- Intestinal Biopsies-variability in interpretation, sampling and the degree of infiltration required for diagnosing mast cell involvement
  - Better to check bone marrow

A Quick Tip for evaluating some patients suspected of having SM

- If no skin lesions of urticaria pigmentosa are present and serum tryptase is < 10 ng/mL
  - Chance of SM is low; no bone marrow is needed
- If no skin lesions of urticaria pigmentosa are present and serum tryptase is >10 ng/mL
  - Check the urinary n-Methyl histamine or MIAA level
  - If elevated, proceed with bone marrow biopsy. If normal, do not proceed with bone marrow biopsy.
  - Van Doormaal JJ et al. Allergy 2012; 67: 683

What to look for

- Urticaria pigmentosa (UP)-most adults with UP have systemic mastocytosis
- Mediator symptoms, other suggestive clinical features (bee sting anaphylaxis, idiopathic anaphylaxis)
- Good response to MC mediator blockade
- Increased (baseline or symptom-associated) mast cell mediator levels:
  - Tryptase> 20 ng/mL;
  - Elevated 24 hour Urinary N-methyl histamine; 11β-PGF2α; LTE4
- Confirmatory: bone marrow biopsy with specific findings
  - Tryptase staining: multifocal dense infiltrates (>15 MCs per aggregate)
  - Mast cell morphology (>25%) show: spindle shape, hypo-granulated cytoplasm, oval decentralized nucleus
  - Mast cell phenotype: (+) CD 25
  - C-kit Asp816Val mutation